REMARKS

It is respectfully requested that this application be reconsidered in view of the above amendments and the following remarks and that all of the claims remaining be allowed.

Claims Amendments:

Claim 25 has been canceled without prejudice or disclaimer as belonging to an unelected group in response to the restriction requirement. Applicants specifically reserve the right of filing one or more continuation or divisional applications directed to the canceled subject matter.

Claim 1 has been amended to recite a method of "preparing a cellular composition with a reduced amount of neoplastic cells". Support for this recitation can be found, for example, in Example 4 (pages 33-34).

Claim 1 has also been amended to recite providing a mixed cellular composition which comprises neoplastic cells and contacting the mixed cellular composition with a virus, wherein the virus is capable of selectively killing the neoplastic cells. Support for these recitations can be found, for example, in Example 4 (pages 33-34).

Claim 1 has further been amended to recite collecting the treated cellular composition "for future use", for which support can be found, for example, at page 21, last paragraph to page 22, first two paragraphs.

In addition, claim 1 has been amended to delete "wherein said composition is" from the preamble and to add "the" in step (a). These amendments do not change the subject matter but improve flow of the claim language.

No new matter has been added by these amendments. The Examiner is hereby requested to enter these amendments.

Restriction Requirement

Applicants confirm the election of Group I, claims 1-24, without traverse. The sole unelected claim, claim 25, has been canceled without prejudice or disclaimer in response to the restriction.

Priority

The Office Action indicates that claims 2-4 are not entitled to the benefit of U.S. Provisional Application No. 60/201,990, filed May 3, 2000 ("the '990 application"). Applicants respectfully traverse.

Claim 2 is directed to a method of selectively removing neoplastic cells from a mixed cellular composition according to claim 1, wherein the mixed cellular composition comprises hematopoietic stem cells. Claims 3 and 4 depend from claim 2, further providing that the hematopoietic stem cells are harvested from bone marrow and blood, respectively. These claims are supported by the '990 application.

The '990 application discloses that a problem that can be solved using the present invention is purging of hematopoietic progenitor stem cells (page 2, lines 7-23, particularly lines 7-11). Accordingly, the ability of reovirus to selectively remove neoplastic cells from a mixture of CD34 positive stem cells and MCF7 neoplastic cells was tested, and the results indicate that MCF7 cells were selectively depleted from the mixture, while the CD34 positive stem cells remained intact (page 4, lines 20-22). Since it was well known at the time the '990 application was filed that CD34 positive stem cells are hematopoietic stem cells which can be harvested from either blood or bone marrow[1], claims 2-4 are supported by the '990 application.

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[1]See, *e.g.*, last paragraph on page 25 to first paragraph on page 26, *Cellular and Molecular Immunology* (Abbas et al., 4th ed.), W.B. Saunders Company, Philadelphia, Pennsylvania. A copy of pages 25-26 is enclosed herewith. Briefly, this reference teaches that all the blood cells originate from a common stem cell that expresses CD34 and stem cell antigen-1. These markers are used to identify and enrich stem cells from suspension of bone marrow or peripheral blood cell for use in bone marrow transplantation.

Accordingly, Applicants respectfully submit that claims 2-4 are entitled to the benefit of the filing date of the '990 application, May 3, 2000.

Rejection Under 35 U.S.C. §112:

A. The rejection of claims 1-24 under 35 U.S.C. §112, first paragraph, as allegedly not being enabled is respectfully traversed as set forth below.

Claim 1 is directed to a method of preparing a cellular composition with a reduced amount of neoplastic cells by selectively removing neoplastic cells from a mixed cellular composition wherein said composition is located outside of a living organism, said method comprising the steps of:

(a) providing a mixed cellular composition which comprises neoplastic cells and contacting the mixed cellular composition with a virus, wherein the virus is capable of selectively killing the neoplastic cells, under conditions which result in substantial killing of the neoplastic cells so as to selectively remove neoplastic cells from the composition; and

(b) collecting the treated cellular composition for future use.

As stated in the Office Action, the test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure in the specification coupled with information known in the art without undue experimentation. *United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988). For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art would expect the claimed genus could be used in that manner without undue experimentation. MPEP §2164.02.

Reovirus is disclosed in the present application as a representative working example. Thus, Example 1 (pages 31-32) describes a method of determining the ability of a virus, in this case reovirus, to kill neoplastic cells. In Examples 2 and 3 (pages 32-33), it is demonstrated that reovirus can be used to selectively inhibit protein synthesis of a

neoplastic cell but not hematopoietic stem cells ($CD34^+$ cells), and that reovirus does not interfere with proliferation and differentiation of $CD34^+$ cells. Example 4 (page 33-34) further describes the method of selectively removing neoplastic cells from a mixed cellular composition that comprises both $CD34^+$ cells and contaminating neoplastic cells to generate a cellular composition with a reduced amount of neoplastic cells.

Although reovirus is used as an example, a person of ordinary skill in the art can follow the instructions of this application and apply the method to purge any mixed cellular composition by using viruses other than reovirus (page 17, lines 22-24 of the specification). The Office Action states that the rejected claims encompass all types of neoplastic cells (page 6 of the Office Action); however, Applicants wish to point out that the claims recite neoplastic cells that can be selectively killed by the virus used. In this regard, the specification provides sufficient guidance as to how to determine if a neoplastic cell can be killed by a virus of interest, for example, in Examples 1 and 2. Furthermore, if the Office Action is concerned about inoperative species, Applicants submit that the claims recite "contacting the mixed cellular composition with a virus, wherein the virus is capable of selectively killing the neoplastic cells, under conditions which result in substantial killing of the neoplastic cells so as to selectively remove neoplastic cells from the composition". Therefore, no inoperative species are encompassed by the claims.

In view of the above, the claims are fully enabled to the extent consistent with their scope and undue experimentation is not necessary. Accordingly, withdrawal of this rejection is respectfully requested.

B. The rejection of claim 1 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite is respectfully traversed for the following reasons.

The Office Action states that it is allegedly unclear if the recitation of "collecting the treated cellular composition" in claim 1 requires an additional step, or if simply treating the cells so as to substantially kill neoplastic cells produces a collection of treated cells. To

emphasize that claim 1 is directed to a method of preparing a cellular composition for future use rather than merely removing neoplastic cells from a composition, claim 1 has been amended to recite "A method of preparing a cellular composition with a reduced amount of neoplastic cells" and that step (b) is "collecting the treated cellular composition for future use".

Applicants respectfully request that this rejection be withdrawn.

Double Patenting

Claims 1-8 and 24 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-8 and 21 of copending application Serial No. 09/847,356 (Patent Application Publication No. 2002/0006398 A1). Applicants will file a terminal disclaimer in due course if appropriate.

Rejection Under 35 U.S.C. §102:

A. The rejection of claims 1, 9-11, 13-15 and 24 under 35 U.S.C. §102(b) in view of McCormick (WO 94/18992) is obviated-in-part and traversed-in-part as set forth below.

The standard of anticipation under 35 U.S.C. §102 is that each and every element of the claim must be found in the cited reference. *In re Marshall* (CCPA 1978), 198 USPQ 344.

Claim 1, as amended, is directed to a method of preparing a cellular composition with a reduced amount of neoplastic cells by selectively removing neoplastic cells from a mixed cellular composition located outside of a living organism, said method comprising the steps of:

(a) providing a mixed cellular composition which comprises neoplastic cells and contacting the mixed cellular composition with a virus, wherein the virus is capable of selectively killing the neoplastic cells, under conditions which

result in substantial killing of the neoplastic cells so as to selectively remove neoplastic cells from the composition; and

(b) collecting the treated cellular composition for future use.

Claims 9-11, 13-15 and 24 all depend from claim 1 and thus contain all the claim elements recited above.

WO 94/18992 relates to methods of ablating neoplastic cells by infecting the neoplastic cells with a recombinant adenovirus with mutated E1A or E1B. With respect to *ex vivo* use, which is required by the claimed invention, WO 94/18992 only teaches diagnostic methods (column 16, lines 26-49 of WO 94/18992). Briefly, WO 94/18992 describes that a cell sample can be infected with a suitable adenovirus, and the cells in the cell sample that express a replication phenotype can be quantified to provide a measure of the amount of neoplastic cells in the sample. WO 94/18992 thus does not contemplate any further use for the treated cells.

In contrast, the present invention relates to a method of preparing a "cleaned up" cellular composition by treating the composition with a virus, and the treated composition can then be subject to further use such as transplantation or cell culture. This claim element is not taught by WO 94/18992.

Accordingly, WO 94/18992 does not teach each and every element of the claimed invention. Therefore, the requirement under 35 U.S.C. §102 is not met, and withdrawal of this rejection is respectfully requested.

B. Similarly, the rejection of claims 1, 9-11, 13-15, 20 and 24 under 35 U.S.C. §102(b) in view of McCormick (U.S. Patent No. 5,801,029, hereinafter referred to as "the '029 patent") is obviated-in-part and traversed-in-part. The '029 patent is similar to WO 94/18992 and does not teach a method of preparing a cellular composition with a reduced amount of neoplastic cells for further use. Accordingly, withdrawal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. §103:

A. The rejection of claims 2-6 and 8 under 35 U.S.C. §103(a) over McCormick (both WO 94/18992 and the '029 patent) in view of Lee et al. (U.S. Patent No. 6,136,307) is respectfully traversed for the reasons set forth below.

To properly issue a rejection under 35 U.S.C. §103, the USPTO bears the initial burden to establish a prima facie case of obviousness by meeting three criteria. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings to arrive at the claimed invention. *In re Vaeck*, 20 USPQ 2d 1438 (Fed. Cir. 1991). Second, there must be a reasonable expectation of success. *Id.* Finally, the prior art reference or the combination of references must teach or suggest all the claim limitations. *In re Royka*, 180 USPQ 580 (CCPA 1974).

This rejection does not meet the criteria required under 35 U.S.C. §103. Claim 2 is directed to a method of preparing purged hematopoietic stem cells, which comprises the steps of:

(a) providing a mixed cellular composition which comprises neoplastic cells and contacting the mixed cellular composition with a virus, wherein the virus is capable of selectively killing the neoplastic cells, under conditions which result in substantial killing of the neoplastic cells so as to selectively remove neoplastic cells from the composition; and

(b) collecting the treated cellular composition for future use.

Claims 3 and 4 depend from claim 2, further requiring that the hematopoietic stem cells be harvested from bone marrow and blood, respectively.

Both of the McCormick references relate to methods of ablating neoplastic cells by infecting the neoplastic cells with a recombinant adenovirus with mutated E1A or E1B. Nowhere do these references teach or suggest that the methods can be used to prepare purged *ex vivo* cellular compositions for future use, let alone hematopoietic stem cells.

Similarly, Lee et al. teach methods of treating proliferative disorders, including hematopoietic neoplasms, with reovirus. However, Lee et al. do not specifically teach or suggest purging any *ex vivo* composition with a virus for future use. Therefore, there is no teaching or suggestion in the references to modify the reference or to combine reference teachings to arrive at the inventions of claims 2-4.

The Office Action states that "The ordinary skilled artisan would have been motivated to make this modification because hematopoietic stem cells can be contaminated with neoplastic cells, therefore a method of killing those neoplastic cells would be beneficial". This statement is based on impermissible hindsight. As discussed above, none of the cited reference teaches or suggests preparation of an *ex vivo* composition for the purpose of future use. Therefore, why would a skilled artisan be motivated to combine the references with the possibility that *ex vivo* hematopoietic stem cells can be contaminated with neoplastic cells? Even if the McCormick references are combined with Lee et al., for which there is no motivation in the first place, motivation or suggestion to modify the combined teaching to arrive at the claimed invention is still missing.

Similarly, claims 5, 6 and 8 relate to methods of preparing cellular compositions that comprise tissues, organs, part thereof, cultured cells, semen or eggs. Again, none of the references teach or suggest a method of preparing cellular compositions for future use, and there is no motivation to combine and/or modify the references to arrive at the claimed invention.

Accordingly, the requirement under 35 U.S.C. §103(a) is not satisfied, and Applicants respectfully request that this rejection be withdrawn.

B. The rejection of claim 7 under 35 U.S.C. §103(a) over McCormick (both WO 94/18992 and the '029 patent) in view of Lee et al. (U.S. Patent No. 6,136,307), and further in view of Bensinger (Bone Marrow Trans. 21: 113-115, 1998), is respectfully traversed for the reasons set forth below.

Claim 7 is directed to a method of preparing an *ex vivo* cellular composition with a reduced amount of neoplastic cells by

(a) providing a mixed cellular composition which comprises neoplastic cells and contacting the mixed cellular composition with a virus, wherein the virus is capable of selectively killing the neoplastic cells, under conditions which result in substantial killing of the neoplastic cells so as to selectively remove neoplastic cells from the composition; and

(b) collecting the treated cellular composition for future use;

wherein the cellular composition comprises a tissue, an organ or any portion of a tissue or an organ, and wherein the tissue, organ or portion of the tissue or organ is useful for transplantation.

The McCormick references and Lee et al. are discussed above and do not specifically teach or suggest the use of a virus to prepare any *ex vivo* cellular composition for transplantation. The Bensinger reference points out the problem of contaminating neoplastic cells in hematopoietic stem cells and the fact that state-of-the-art purging methods had adverse effects. In fact, those purging methods appeared to be so unsatisfactory that Bensinger questions the wisdom of purging at all, thereby teaching away from the claimed invention. Thus, the references, either alone or in combination, do not teach or suggest the claimed invention or provide a motivation to combine, modify and arrive at the claimed invention.

On the contrary, these references support novelty and non-obviousness of the present invention. As taught by Bensinger, contamination of hematopoietic cells had been a problem and no good purging method was available. If, as the Office Action alleges, it had been obvious to combine these references to arrive at the present invention, the present invention would have been developed long ago since there was a long-felt need for a good purging method.

Therefore, withdrawal of this rejection is respectfully requested.

C. The rejection of claim 12 under 35 U.S.C. §103(a) over McCormick (both WO 94/18992 and the '029 patent) in view of Strong et al. (EMBO J. 17(12):3351-3362, 1998) is respectfully traversed for the reasons set forth below.

Claim 12 relates to preparation of an *ex vivo* cellular composition having a reduced amount of neoplastic cells for future use by

(a) providing a mixed cellular composition which comprises neoplastic cells and contacting the mixed cellular composition with a virus, wherein the virus is capable of selectively killing the neoplastic cells, under conditions which result in substantial killing of the neoplastic cells so as to selectively remove neoplastic cells from the composition; and

(b) collecting the treated cellular composition for future use;

wherein the virus is mutated or modified such that the virus does not produce a gene product which inhibits double stranded RNA kinase (PKR).

The McCormick references, described above, suggest that certain adenovirus can be used for treating animals or diagnosis of cancer. However, these references do not teach or suggest any method for preparing an *ex vivo* cellular composition for future use. Strong et al. teach the relationship of PKR and the ras pathway, but Strong et al. do not teach or suggest that a virus can be used to prepare any *ex vivo* cells for future use. Therefore, the references, either alone or in combination, do not teach or suggest all the elements of claim 12, in particular the preparation of an *ex vivo* composition that can be of further use. In addition, there is no motivation or suggestion to combine and modify the references in the first place since none of the references relates, in any manner, to the use of a virus to purge a cellular composition.

Accordingly, withdrawal of this rejection is respectfully requested.

D. The rejection of claims 16-19 under 35 U.S.C. §103(a) over McCormick (both WO 94/18992 and the '029 patent) in view of Stodjl et al. (Nature Medicine 6(7):821-825, 2000) is respectfully traversed for the reasons set forth below.

Claims 16-19 relate to preparation of *ex vivo* cellular compositions having a reduced amount of neoplastic cells for future use, wherein a virus and interferon are added to the cellular composition.

The McCormick references, described above, suggest that certain adenovirus can be used for treating animals or diagnosis of cancer. However, these references do not teach or suggest any method for preparing an *ex vivo* cellular composition for future use. Stojdl et al. teach that the vesicular stomatitis virus (VSV) can be used along with interferon to treat interferon-non-responsive tumors. Like the McCormick references, Stojdl et al. do not teach or suggest any method for preparing a cellular composition for future use. Since none of the references teaches or suggests this required element, combining the references does not cure the deficiency. In addition, there is no motivation or suggestion to combine and modify the references in the first place since none of the references relates, in any manner, to the use of a virus to purge a cellular composition.

Accordingly, the requirement under 35 U.S.C. §103(a) is not satisfied, and Applicants respectfully request that this rejection be withdrawn.

E. The rejection of claims 22 and 23 under 35 U.S.C. §103(a) over McCormick (both WO 94/18992 and the '029 patent) in view Stewart et al. (Bone Marrow Trans. 23:111-117, 1999) is respectfully traversed for the reasons set forth below.

Claims 22 and 23 relate to preparation of an *ex vivo* cellular composition having a reduced amount of neoplastic cells for future use by

(a) providing a mixed cellular composition which comprises neoplastic cells and contacting the mixed cellular composition with a virus, wherein the virus is capable

of selectively killing the neoplastic cells, under conditions which result in substantial killing of the neoplastic cells so as to selectively remove neoplastic cells from the composition; and

(b) collecting the treated cellular composition for future use;

wherein the virus treated cellular composition is stored before future use, for example, in a DMSO solution.

The McCormick references, described above, suggest that certain adenovirus can be used for treating animals or diagnosis of cancer. However, these references do not teach or suggest any method for preparing an *ex vivo* cellular composition for future use. Stewart et al. teach storage of stem cells in a DMSO solution. Like the McCormick references, Stewart et al. do not teach or suggest any method for preparing a cellular composition for future use. Since none of the references teaches or suggests this required element, combining the references does not cure the deficiency. In addition, there is no motivation or suggestion to combine and modify the references in the first place since none of the references relates, in any manner, to the use of a virus to purge a cellular composition.

Accordingly, the requirement under 35 U.S.C. §103 is not satisfied, and Applicants respectfully request the withdrawal of these rejections.

Conclusions:

For the reasons set forth above, Applicants submit that the claims of this application are patentable. Reconsideration and withdrawal of the Examiner's rejections are hereby requested. Allowance of the claims remaining in this application is earnestly solicited.

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is requested to call the undersigned at (650) 622-2340.

Respectfully submitted,

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Attachment to Amendment dated December 5, 2002
Marked-up Copy
Claim 1

1. (amended) A method of preparing a cellular composition with a reduced amount of neoplastic cells by selectively removing neoplastic cells from a mixed cellular composition [wherein said composition is] located outside of a living organism, said method comprising the steps of:

(a) providing a mixed cellular composition which comprises neoplastic cells and contacting the mixed cellular composition with a virus, wherein the virus is capable of selectively killing the neoplastic cells, under conditions which result in substantial killing of the neoplastic cells so as to selectively remove neoplastic cells from the composition; and

(b) collecting the treated cellular composition for future use.

FOURTH EDITION

CELLULAR AND MOLECULAR IMMUNOLOGY

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are initiated and develop (see Fig. 2–2). Included in the generative lymphoid organs of mammals are the bone marrow, where all the lymphocytes arise, and the thymus, where T cells mature and reach a stage of functional competence. The peripheral lymphoid organs and tissues include the lymph nodes, spleen, cutaneous immune system, and mucosal immune system. In addition, poorly defined aggregates of lymphocytes are found in connective tissue and in virtually all organs except those in the central nervous system.

Bone Marrow

The bone marrow is the site of generation of all circulating blood cells in the adult, including immature lymphocytes, and is the site of B cell maturation. During fetal development, the generation of all blood cells, called **hematopoiesis,** occurs initially in blood islands of the yolk sac and the para-aortic mesenchyme and later in the liver and spleen. This function is taken over gradually by the bone marrow and increasingly by the marrow of the flat bones, so that by puberty hematopoiesis occurs mostly in the sternum, vertebrae, iliac bones, and ribs. The red marrow that is found in these bones consists of a spongelike reticular framework located between long trabeculae. The spaces in this framework are filled with fat cells, stromal fibroblasts, and precursors of blood cells. These precursors mature and exit via the dense network of vascular sinuses to enter the vascular circulation. When the bone marrow is injured or when an exceptional demand for production of new blood cells occurs, the liver and spleen can be recruited as sites of extramedullary hematopoiesis.

All the blood cells originate from a common **stem cell** that becomes committed to differentiate along particular lineages (i.e., erythroid, megakaryocytic, granulocytic, monocytic, and lymphocytic) (Fig. 2–7). This stem cell lacks the markers of differentiated

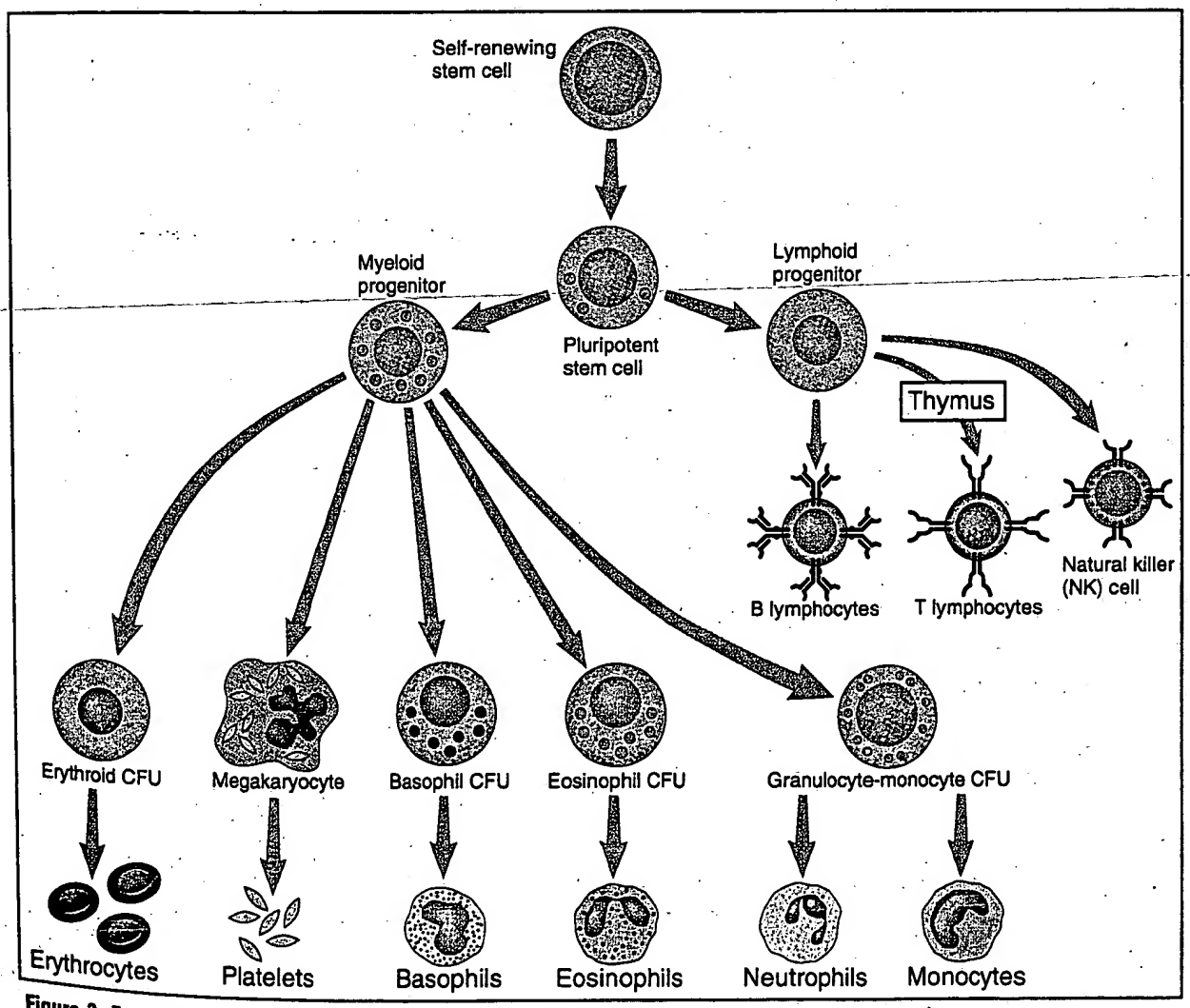

Figure 2–7 Hematopoiesis.
The development of the different lineages of blood cells is depicted in this "hematopoietic tree." The regulation of hematopoiesis by cytokines is illustrated in Chapter 11, Figure 11–18. CFU, colony-forming unit.

blood cells and instead expresses two proteins called CD34 and stem cell antigen-1 (Sca-1). These markers are used to identify and enrich stem cells from suspensions of bone marrow or peripheral blood cells for use in bone marrow transplantation. The proliferation and maturation of precursor cells in the bone marrow are stimulated by cytokines. Many of these cytokines are also called colony-stimulating factors (CSFs) because they were originally assayed by their ability to stimulate the growth and development of various leukocytic or erythroid colonies from marrow cells. These molecules are discussed in Chapter 11 (see Fig. 11–18). Hematopoietic cytokines are produced by stromal cells and macrophages in the bone marrow, thus providing the local environment for hematopoiesis. They are also produced by antigen-stimulated T lymphocytes and cytokine-activated or microbe-activated macrophages, providing a mechanism for replenishing leukocytes that may be consumed during immune and inflammatory reactions.

In addition to self-renewing progenitors and their differentiating progeny, the marrow contains numerous antibody-secreting plasma cells, which develop in peripheral lymphoid tissues as a consequence of antigenic stimulation of B cells and then migrate to the marrow. The maturation of T lymphocytes occurs not in the bone marrow but in the thymus.

Thymus

The thymus is the site of T cell maturation. The thymus is a bilobed organ situated in the anterior mediastinum. Each lobe is divided into multiple lobules by fibrous septa, and each lobule consists of an outer cortex and an inner medulla (Fig. 2–8). The cortex contains a dense collection of T lymphocytes, and the lighter staining medulla is more sparsely populated with lymphocytes. Scattered throughout the thymus are nonlymphoid epithelial cells, which have abundant cytoplasm, as well as bone marrow–derived macrophages and dendritic cells. Some of these thymic dendritic cells are derived from T lymphocyte precursors and are called lymphoid dendritic cells to distinguish them from the myeloid dendritic cells described earlier. In the medulla are structures called Hassall's corpuscles, which are composed of tightly packed whorls of epithelial cells that may be remnants of degenerating cells. The thymus has a rich vascular supply and efferent lymphatic vessels that drain into mediastinal lymph nodes. The thymus is derived from invaginations of the ectoderm in the developing neck and chest of the embryo, forming structures called branchial clefts. The formation of the thymus is not dependent on hematopoietic cells, which populate the developing thymus by migration from the bone marrow. In the "nude" mouse strain, a mutation in the gene encoding a transcription factor causes a failure of differentiation of certain types of epithelial cells that are required for normal development of the thymus and hair follicles. Consequently, these mice lack T cells and hair (see Chapter 20). Humans with DiGeorge syndrome also suffer from T cell deficiency because of mutations in genes required for thymus development.

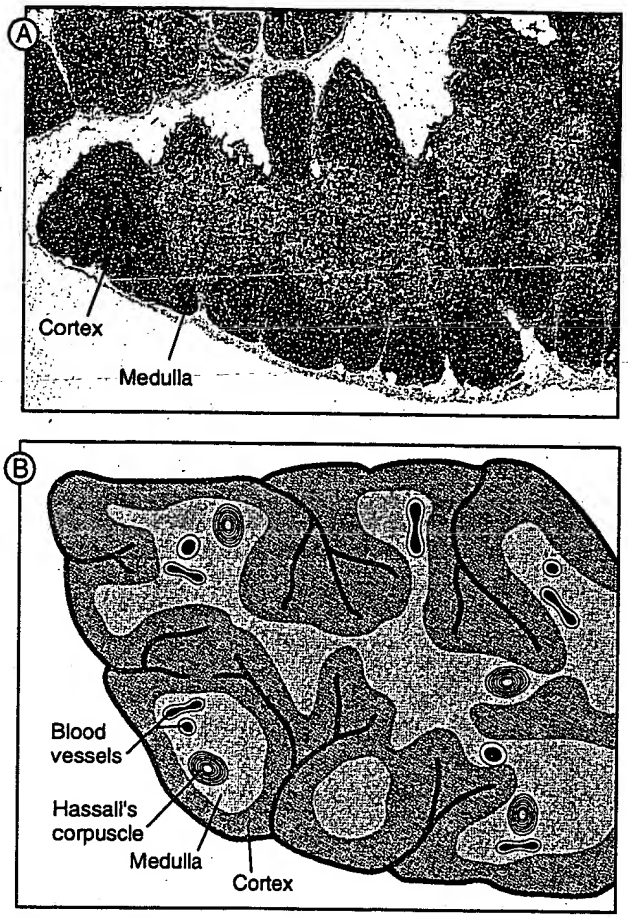

Figure 2–8 Morphology of the thymus.
A. Light micrograph of a lobe of the thymus, showing the cortex and medulla. The blue-stained cells are developing T cells called thymocytes. (Courtesy of Dr. James Gulizia, Department of Pathology, Brigham and Women's Hospital, Boston.)
B. Schematic diagram of the thymus, illustrating a portion of a lobe divided into multiple lobules by fibrous trabeculae.

The lymphocytes in the thymus, also called **thymocytes,** are T lymphocytes at various stages of maturation. In general, the most immature cells of the T cell lineage enter the thymic cortex via the blood vessels. Maturation begins in the cortex, and as thymocytes mature, they migrate toward the medulla, so that the medulla contains mostly mature T cells. Only mature T cells exit the thymus and enter the blood and peripheral lymphoid tissues. The details of thymocyte maturation are described in Chapter 7.

Lymph Nodes and the Lymphatic System

Lymph nodes are the sites where adaptive immune responses to lymph-borne protein antigens are initiated. Lymph nodes are small nodular aggregates of lymphocyte-rich tissue situated along lymphatic channels throughout the body. Each lymph node is surrounded by a fibrous capsule that is pierced by numerous afferent lymphatics, which empty the